REMARKS

Claims 1-47 remain pending after entry of this amendment. Claims 8 and 9 were amended herein. Favorable reconsideration is respectfully requested in light of the amendments and remarks submitted herein.

Claims 8 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

Claims 1-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,817,042 (Langley) in view of U.S. 4,708,714 (Larsson). Applicant respectfully traverses this rejection.

Rejection under 35 U.S.C. § 112

Claims 8 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner notes that the claims recite the limitations "said calcium compound" and "said magnesium compound". Claims 8 and 9 have been amended to refer to "said antidote", for which there is sufficient antecedent basis. In light of the amendment to claims 8 and 9, Applicant respectfully requests that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,817,042 (Langley) in view of U.S. 4,708,714 (Larsson). The Examiner asserts that Langley discloses a method and apparatus for withdrawing blood from any donor or patient, adding a citrate-containing anticoagulant, separating the blood component parts, and returning some portion of the blood to the patient along with a replacement fluid (cites to Fig 1, columns 5-7). The Examiner further asserts that Langley also discloses that the amount of anticoagulant administered is calculated, varied, and controlled according to the needs of the patient and the desired procedure, since a patient cannot tolerate unmitigated doses of citrate-based anticoagulants. The Examiner then admits that Langley fails to disclose that the replacement fluid contains an "antidote" to the anticoagulant.

However, the Examiner also asserts that Larsson discloses a blood separation system that uses a calcium solution from a source to neutralize the anticoagulant citrate solution before returning blood to the patient. The Examiner therefore asserts that it would have been obvious to one of ordinary skill in the art to add a calcium or other anticoagulant-neutralizing solution as disclosed by Larsson to the replacement fluid in the apheresis system disclosed by Langley in order to neutralize the anticoagulant and prevent citrate-induced harmful effects in the patient.

Langley, teaches only control of the amount of citrate given to the patient/donor, and does not teach administration of an antidote. Langley teaches limiting the amount of citrate. Langley did not teach use of an antidote or neutralization. Langley teaches the details of administration of only a single agent, which is adjusted by limiting the rate of infusion so that a maximum allowable donor/patient estimated citrate concentration ("MADEC") is not exceeded. Column 7 line 60. Langley did not disclose antidote, Langley did not claim antidote, the calculation of Langley teaches the importance of limiting the anticoagulant rate so that the maximum safe concentration of anticoagulant in the donor blood is not exceeded.

Larsson teaches use of an "antidote", for the plasma portion of a separated blood product but does not couple the administration of the antidote to the administration of the anticoagulant. Indeed, Larsson, in column 5 teaches only that "Before any PLASMA is returned to the patient, this citrate solution is neutralized with the help of a calcium solution from a source 18, which is connected to a drip chamber 10 through line 19." Although Larsson mentions neutralization of plasma, it does not show how such neutralization would occur nor does it discuss dosage amounts. Larsson mentions a "drip chamber" but does not teach any stochiometric connection between the neutralizing agent and the citrate. Furthermore, Larsson gives no means for metering the neutralizing solution. One skilled in the art might expect to see spontaneous coagulation within a drip chamber which did not include means of mixing and emptying. There is no indication that Larsson considered coupling or correlating the calcium in this "drip chamber" delivery system to the Citrate delivery system (17) which is itself not connected to the withdrawal pump (5). This shows that there was no intent to link the delivery of a neutralizing solution to the citrate delivery system. Larsson teaches no reason for neutralization and neutralization appears to have had no function within the Larsson invention. Furthermore, Larsson's apparatus relates to the field of therapeutically removing antibodies from plasma utilizing adsorption columns, a process that is somewhat removed from the invention of Langley.

Applicant respectfully asserts that the Examiner has failed to establish a *prima facie* case of obviousness. In order to establish *prima facie* obviousness, three basic criteria must be met, namely: (1) there must be some suggestion or motivation to combine the references or modify the reference teaching; (2) there must be a reasonable expectation of success; and (3) the reference or references when combined must teach or suggest each claim limitation. Applicant submits that the Office Action failed to state a *prima facie* case of obviousness, and therefore the burden has not properly shifted to Applicant to present evidence of nonobviousness.

Applicant respectfully asserts that there is not suggestion or motivation to combine the references. The Examiner apparently asserts that one of skill in the art would have been motivated to combine Langley with Larsson in order to "neutralize the anticoagulant and prevent citrate-induced harmful effects in the patient". Applicant respectfully disagrees with the Examiner regarding this point because Langley already addressed this problem, and one of skill in the art, given the disclosure of Langley, would not have been faced with this problem. The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. Applicant respectfully asserts that Langley did not suggest the modification, as the Examiner asserts it did, because the problem supposedly addressed would already have been overcome by Langley. Larsson also offers no motivation for the combination of the references, because it fails to even provide any indication of why the citrate is being neutralized.

Langley teaches specific and accurate control of the amount of citrate given to the patient/donor as a method of maximizing the amount of blood processed without exceeding a tolerable level of anticoagulant. Langley teaches that once this tolerable amount is exceeded, the donor/patient will experience adverse physiological side effects. Therefore, Langley avoids any side effects by precise control and adjustment of the anticoagulant level. Therefore, one of skill in the art, given the teachings of Langley, would not be forced to address the problem of "neutralizing the anticoagulant and prevent citrate-induced harmful effects in the patient". Indeed, the very problem that the Examiner asserts would motivate one of skill in the art to look to Larsson is already solved by Langley.

Indeed, Langley fails to discuss, or suggest the use of an antidote to the anticoagulant, because the problems associated with excess anticoagulant are not encountered in Langley

because the rate of anticoagulant administration is so precisely controlled. Langley not only fails to teach that any antidote might be given but entirely concentrates on the administration rate of citrate and its effect on the patient. In column 2 Langley teaches that "the rate at which the anticoagulant is returned or infused back to the donor/patient during blood processing procedures is not too rapid. Infusing anticoagulant to a donor/patient more rapidly than it can be removed by the donor/patient's metabolic, renal or other clearance process will result in an increase in the level or concentration in the donor or patient." Therefore, Langley simply avoids infusion that is too rapid. Because Langley concentrated on precise and patient specific control of anticoagulant levels, Langley never even considered that an antidote could be given.

Applicant also asserts that there is no motivation to modify or combine the teachings of Langley and Larsson because introduction of the neutralization concept of Larsson into Langley's process would make the method of Langley unfit for its intended purpose. The method of Langley depends on the consideration of a very large number of quantitative parameters, including: TBV (patient's total blood volume), patient's interstitial fluid, patient's intracellular fluid, blood volume of tubing set, whole blood flow, anticoagulated blood flow in the inlet line, anticoagulant flow from the anticoagulant reservoir to the inlet line, collected blood component flow, return blood flow, etc. (see column 8, line 48 - column 9, line 56 and FIG 2). Clearly, the equations and relationships set out by Langley are very intricate and consider a great number of details. Introduction of an antidote to the anticoagulant would most assuredly have an effect on the numerous parameters, and the interplay between those parameters. Such an introduction, without a detailed consideration of its effects, and a profound reworking of the relationships involved in Langley would certainly lead to a failure of Langley to fulfill its intended purpose. More than likely, the introduction of the antidote would be so upsetting to the relationships of Langley, that it would not be able to be reworked. Either way the introduction of the antidote would more than likely leave the method of Langley unable to function for its intended purpose, and therefore, according to MPEP § 2143.01, there is no motivation to combine these references.

Applicant also respectfully asserts that the Examiner has failed to establish a *prima facie* case of obviousness because the references when combined fail to teach or suggest all of the elements. Specifically, the Applicant asserts that the combination of the references fail to teach or suggest coupling the amount of antidote to the amount of anticoagulant.

As a preliminary matter, the Applicant wishes to clarify "coupled" as it is used in this application. Coupling the two agents is discussed at least on page 11, lines 17-28. There, it is stated that

> "the coupling of one agent to another generally means that the delivered amount of one agent is dependent, at least in part, on the delivered amount of another agent. Coupling can be done by mechanical, hydraulic, or electrical means. Coupling can also be accomplished by correlating the concentration of the two agents together so that the delivered amount of one is related to the delivered amount of the other agent." (page 11, lines 18-23).

Coupling can also be thought of as the concept that the delivery of the antidote is related to the delivery of the anticoagulant in a stoichiometric manner. None of the cited references disclose or suggest either the concept of coupling the anticoagulant with an antidote, or an apparatus that would be capable of coupling the anticoagulant to an antidote. Therefore, neither Langley, Larsson, nor the combination thereof discloses this element of the invention.

Based on the comments offered above, Applicant respectfully asserts that the Examiner has failed to establish a *prima facie* case of obviousness, and therefore Applicant requests that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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